Synthesis of N-Urethane Protected α-Aminoalkyl-α′-cyanomethyl Ketones; Application to the Synthesis of 3-Substituted 5-Amino-1*H*-pyrazole Tethered Peptidomimetics

M. K. Sharnabai, G. Nagendra, Vommina V. Sureshbabu*

#109, Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University, Dr. B. R. Ambedkar Veedhi, Bangalore 560 001, India

Received: 05.04.2012; Accepted after revision: 08.06.2012

Abstract: The preparation of N-protected amino/peptide α-cyanomethyl ketones through cyanation of the corresponding α-bromomethyl ketones is described. The utility of the resulting α-cyanomethyl ketones in the synthesis of 3-substituted-5-amino-1*H*-pyrazoles has also been demonstrated. In both steps a wide range of N-protected amino/peptide acids has been employed and the products are obtained in good yield. The enantiomeric purity of both the α-cyanomethyl ketones and pyrazoles were confirmed by chiral HPLC analysis of the corresponding Z-protected D- and L-Ala-OH as model substrates. The synthesis of peptide pyrazolecarboxamides is also delineated.

Key words: peptidomimetics, amino acid mimics, ketones, pyrazole

An important aspect of peptidomimetic design involves the use of suitable building blocks. To this end, either the -NH_2 or -COOH group of enantiopure α-amino acids are converted into the desired functionality. Among them, azides,[1] isonitriles,[2] nitriles,[3] and acetylenes[4] have been generated at the amine or acid termini of α-amino acids. Employing these key constituents, the insertion of scaffolds such as a tetrazole, thiazole, imidazole, triazole, and oxadiazole in place of the peptide bond has also been a subject of interest, particularly for studying the physiochemical and biological properties of peptides (Figure 1).[5–8]

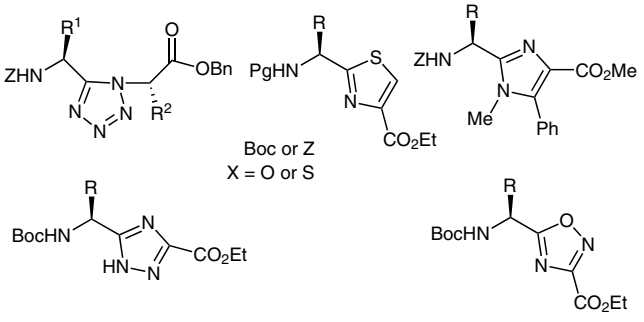


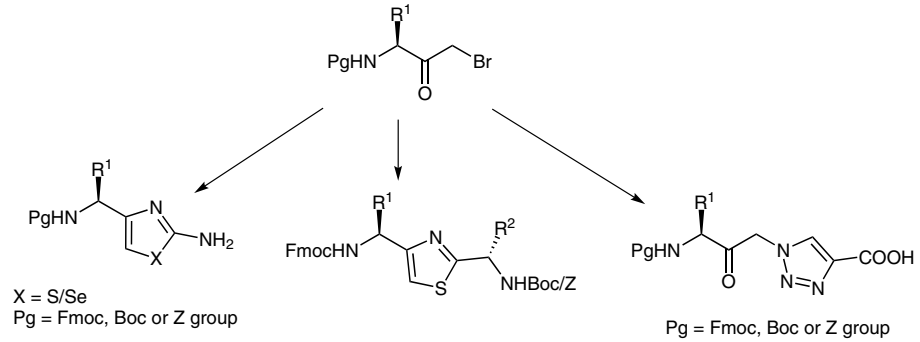
Figure 1 Selected examples of N-heterocycles derived from amino acids

N-Protected α-aminoalkyl-α′-halomethyl ketones[9] have emerged as attractive targets for the design of peptidomimetics.[10–12] Our group has developed a simple route for the preparation of N-protected α-aminoalkyl-α′-halomethyl ketones and employed them for the construction of thiazole,[13] selenazole,[14] and triazole[15] tethered peptidomimetics (Scheme 1).

In the present letter we describe the synthesis of N-urethane protected α-aminoalkyl-α′-cyanomethyl ketones and their utility in the synthesis of amino acid derived 3-substituted 5-amino-1*H*-pyrazoles. The α-cyanomethyl ketone is an important scaffold that is found in many pharmaceutical compounds[16] with a broad spectrum of biological activity.[17,18] Sauve et al. reported amino acid derived α-cyanomethyl ketones and carboxy group modified dipeptides.[19] Boc/Ac-protected Phe/Leu-Phe derived cyanomethyl ketones were synthesized through alkylation of Boc/Ac-amino thioamide with methyl triflate and the resulting intermediate was treated with a nucleophile. *N*-Acetyl protected cyanomethyl ketones have also been prepared by the reaction of activated carboxylic acids and the carbanion of *tert*-butyl cyanoacetate, and the resulting enols were then subjected to hydrolysis followed by decarboxylation.[20] α-Cyanomethyl ketones derived from *N*,*N*′-bisbenzyl protected benzyl phenyl alaninate was prepared by the reaction of MeCN and $NaNH_2$.[21] Some of the above approaches either require a cumbersome protocol or are incompatible with the use of urethane-type protecting groups. We describe herein a convenient method for the synthesis of urethane-protected α-cyanomethyl ketones and their conversion into *N*-Boc/Z-protected α-aminoalkyl-5-amino pyrazoles. Pyrazole[22] derivatives of α-amino acids have received considerable attention because of their diverse range of biological properties such as potent angiotensin II antagonist activity both in vitro and in vivo,[23] anti-hypertensive, anti-bacterial, and anti-inflammatory activity,[24] muscle relaxant properties, and inhibition of cyclin dependent kinases.[25] They have also been used as building blocks for the synthesis of peptidomimetics.[26,27]

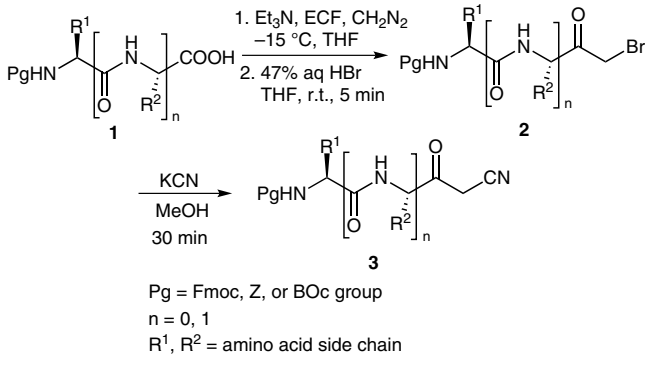
The required urethane-protected α-aminoalkyl-α′-bromomethyl ketone precursors were prepared by using a two-step procedure reported by our group.[13] A similar approach was employed for the preparation of bromomethyl ketones containing the Boc-protected compounds with suitable modifications.[28] In all cases, bromomethyl ke-

SYNLETT 2012, 23, 1913–1918
Advanced online publication: 23.07.2012
DOI: 10.1055/s-0032-1316586; Art ID: ST-2012-D0308-L



Scheme 1 Various transformations of N-protected α-aminoalkyl-α′-halomethyl ketones reported by our group

tones were obtained as stable solids without the need for column purification. The resulting α-bromomethyl ketones were then converted into α-cyanomethyl ketones. We initially investigated the use of several cyanating reagents by using different solvents; the results are summarized in Table 1. Boc-Ala-[CH_2Br] **2a** (Scheme 2) was used as a model substrate to optimize the reaction conditions, with the progress of the reaction being monitored by TLC. Treatment of **2a** with TMSCN in MeOH failed to give **3a** at room temperature (Table 1, entry 1), but under reflux conditions the product was obtained in 20% yield (Table 1, entry 2). We then explored the use of NaCN, HgCN, $K_3Fe(CN)_6$ and KCN at room temperature in MeOH (Table 1, entries 3–6). KCN turned out to be the most useful to obtain **3a**. Furthermore, we examined a range of solvents with the aim of stabilizing the reaction conditions and found that use of THF and CH_3CN led to the formation of **3a** in moderate yield (Table 1, entries 7 and 8), DMF and DMSO gave acceptable yields of **3a** (68 and 72% respectively; Table 1, entries 9 and 10), but the use of MeOH provided an excellent yield of **3a** at room temperature (Table 1, entry 6).



Scheme 2 Synthesis of N-protected α-aminoalkyl or peptidyl cyanomethyl ketones **3**

Under the optimized conditions, reactant **2a** was completely consumed, as evidenced by IR and RP-HPLC analysis. The disappearance of the strong IR absorption band at 1730 cm^{-1} for the α-bromomethyl ketone **2a** and the appearance of strong bands at 1650 and 2243 cm^{-1} for the carbonyl and adjacent nitrile groups, respectively, confirmed the formation of **3a**. The protocol was further applied to various N-protected amino/peptide α-bromomethyl ketones to obtain the corresponding cyanomethyl ketones (Table 2).[29] The procedure worked well even for amino acids Ser and Thr, which contain free hydroxyl groups (Table 2, entries 9, 13, and 15).

Table 1 Screening of Cyanating Agents and Solvents for the Synthesis of **3a**[a]

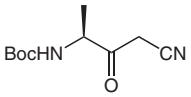
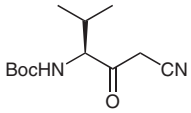
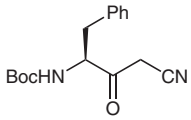
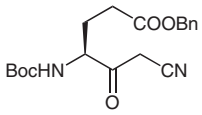
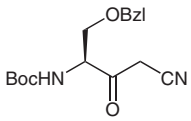
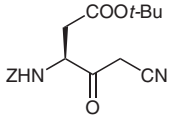
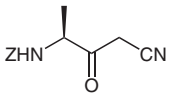
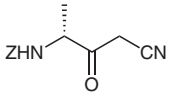
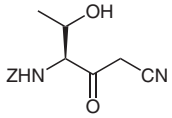
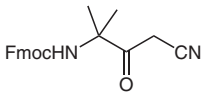
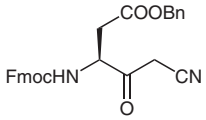
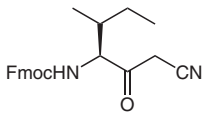
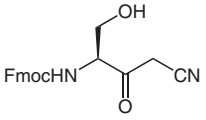
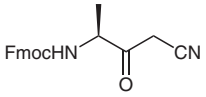
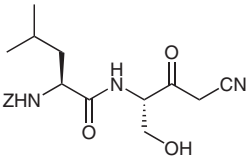
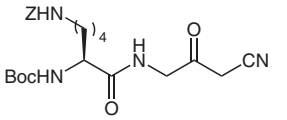
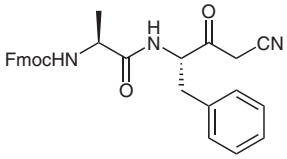
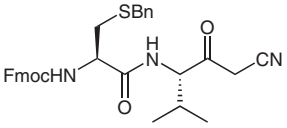
Entry[a]	Cyanating reagent	Solvent	Temp (°C)	Yield (%)[b]
1	TMSCN	MeOH	25	–
2	TMSCN	MeOH	60	20
3	NaCN	MeOH	25	38
4	HgCN	MeOH	25	49
5	$K_3Fe(CN)_6$	MeOH	25	55
6	KCN	MeOH	25	91
7	KCN	THF	35	40
8	KCN	MeCN	25	45
9	KCN	DMF	40	68
10	KCN	DMSO	40	72

[a] Boc-Ala-CH_2Br **2a** (1.0 mmol) was treated with cyanating reagent (1.2 mmol).
[b] Yield of isolated product **3a** after column purification.

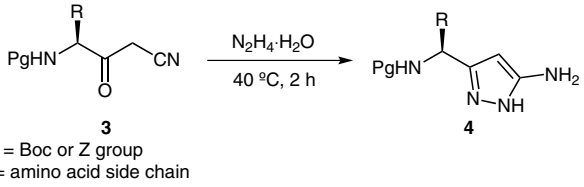
Next, we turned our attention to the synthesis of a hitherto unreported class of N^{α}-Boc/Z-aminoalkyl-5-amino pyrazoles.[30] The 3-substituted 5-amino-1*H*-pyrazole derivatives **4** were prepared by reaction of α-cyanomethyl ketones **3** with hydrazine hydrate under reflux in MeOH (Scheme 3). In a typical experiment, Boc-Ala-[CH_2CN] **3a** was added to a solution of 99–100% hydrazine hydrate in MeOH. The reaction mixture was heated to reflux at 40 °C for approximately two hours. After completion of the reaction (TLC analysis), the solvent was evaporated under reduced pressure and the residue was purified by column chromatography to afford **4a**.[31] Several Boc and Z-protected α-aminoalkyl-α′-cyanomethyl ketones were

converted into their respective pyrazole derivatives **4a–i** in good yield and purity (Table 3).

Table 2 List of N^{α}-Z/Boc-Protected α-Cyanomethyl Ketones **3a–r**

Entry	Product **3**	$[\alpha]_D^{25}$ (c 1, $CHCl_3$)	Yield (%)[a]
1	**3a** 	–14.2	89
2	**3b** 	–12.1	88
3	**3c** 	–21.2	90
4	**3d** 	–15.3	87
5	**3e** 	–13.4	89
6	**3f** 	–16.7	90
7	**3g** 	–18.3	91
8	**3h** 	+21.6	90
9	**3i** 	–22.1	88
10	**3j** 	–12.5	80
11	**3k** 	–13.9	78
12	**3l** 	–17.2	89
13	**3m** 	–14.8	79
14	**3n** 	–20.4	80
15	**3o** 	–15.7	82
16	**3p** 	–13.6	84
17	**3q** 	–16.2	81
18	**3r** 	–18.2	79

[a] Isolated yield.



Scheme 3 Synthesis of N-protected 3-substituted 5-amino-1*H*-pyrazoles **4**

Similarly, two examples of N^{α}-Boc/Z-protected peptidyl 3-substituted 5-amino-1*H* pyrazoles **4j–k** were also prepared (Figure 2). Both cyanomethyl ketones and pyrazole derivatives were characterized by mass, IR and NMR analyses.

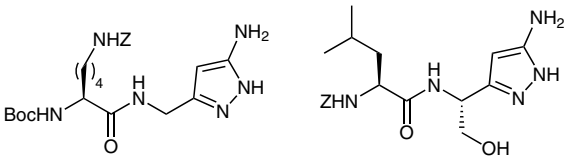


Figure 2 Dipeptidyl pyrazoles synthesized

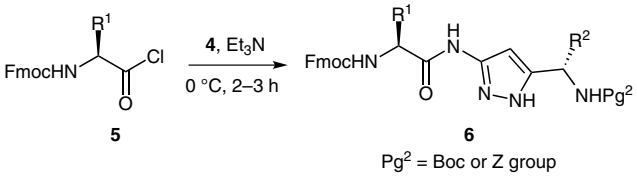
In order to gain insight into the possibility of racemization, enantiomeric Z-protected D- and L-Ala-OH were

converted into cyanomethyl ketones and pyrazoles under the developed reaction conditions, and their enantiomeric excess was determined by chiral HPLC analysis.[32] As shown in Figure 3, compounds **3g** and **3h** showed single peaks with retention times of 28.1 and 22.5 min, respectively.

In contrast, the constituents of the racemic mixture of **3g** and **3h** were separated with retention times of 27.8 and 21.9 min. Similarly, HPLC profiles for pyrazoles **4g** and **4h** showed retention times of 16.9 and 10.1 min, respectively. Thus, these results confirm that both α-cyanomethyl ketones and pyrazoles were prepared in optically pure form.

Finally, the synthesis of pyrazole-linked dipeptidomimetics was undertaken. Pyrazolecarboxamide derivatives are known for their use in the treatment of pain and inflammation[33] and also play a vital role in the β-sheet stabilization of peptides.[34] Thus, pyrazoles **4** were employed to synthesize peptide-derived pyrazolecarboxamides **6**.

As a test case, a solution of Fmoc-Val-Cl[35] in anhydrous THF, Boc-Ala-pyrazole amine **4a** and NMM were reacted at 0 °C. The coupling was found to be complete in three hours, as observed by TLC analysis (Scheme 4).



Scheme 4 Synthesis of pyrazole-tethered peptidomimetics

The desired N,N′-orthogonally protected dipeptidomimetic **6a**[36] was isolated in 88% after column purification. As

Table 3 Data for 3-Substituted 5-Amino-1*H*-pyrazole Derivatives **4a–i**

4	PG	R	HRMS [M + Na]$^+$		Yield (%)[a]	$[\alpha]_D^{25}$ (*c* 1, $CHCl_3$)
			Calcd	Found		
4a	Boc	Me	249.1327	249.1230	85	–12.1
4b	Boc	*i*-Pr	277.1640	277.1643	88	–15.3
4c	Boc	Bn	325.1638	325.1640	92	–17.2
4d	Boc	*i*-Bu	291.1793	291.1791	94	–14.5
4e	Boc	CH_2OH	355.1748	355.1746	92	–10.9
4f	Z	CH_2COO*t*-Bu	505.1849	253.1852	91	–29.5
4g	Z	Me	359.1481	359.1484	90	–13.5
4h	Z	Me[b]	248.1241	248.1249	88	–14.9
4i	Z	$CH(CH_3)OH$	445.1856	455.1852	87	–16.2

[a] Isolated yield.
[b] Z-D-Ala-OH was used as starting compound.

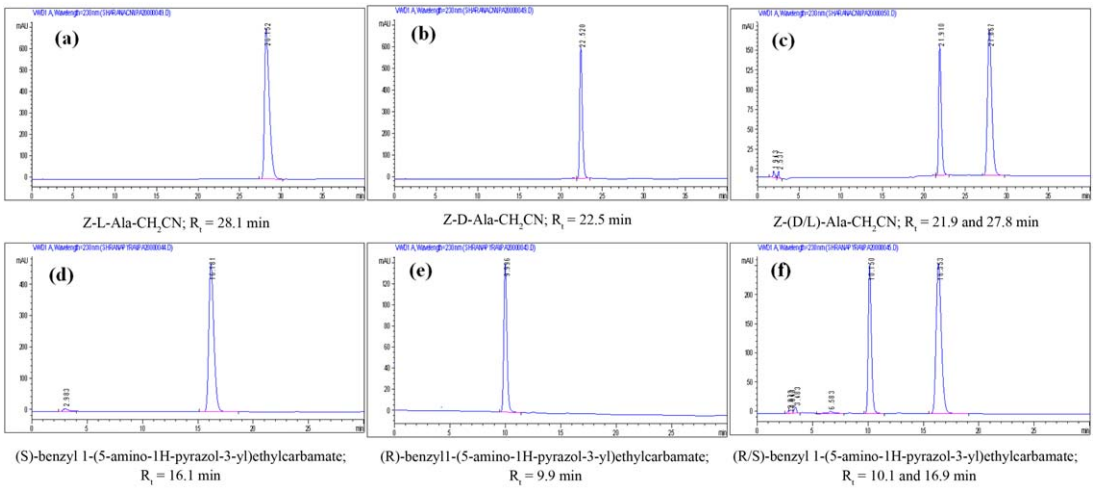


Figure 3 Chiral HPLC analysis.[32] Chromatograms shown are: (a) Z-L-Ala-CH_2CN **3g**; (b) Z-D-Ala-CH_2CN **3h**; (c) Prepared 1:1 mixture of **3g** and **3h**; (d) Z-L-Ala-pyrazole **4g**; (e) Z-D-Ala-pyrazole **4h**; (f) Prepared 1:1 mixture of **4g** and **4h**.

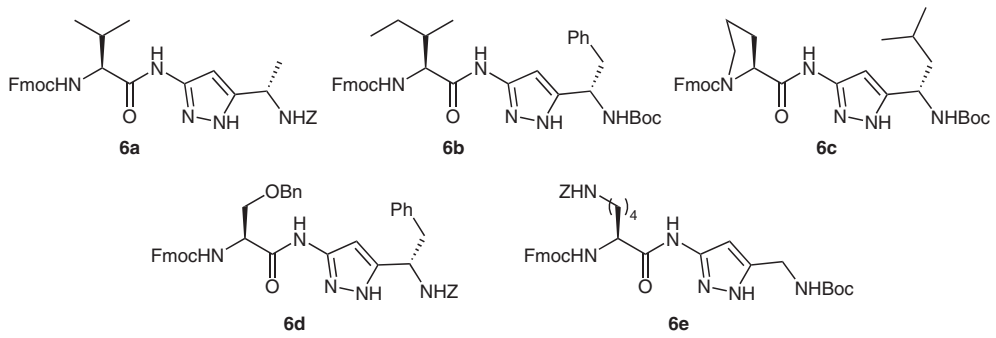


Figure 4 List of pyrazolecarboxamide peptidomimetics **6**

shown in Figure 4, the same procedure was extended to the synthesis of compounds **6b**–**e**.

In summary, a simple and easily accessible route has been established for the synthesis of enantiopure *N*-urethane-protected amino acid/peptidyl cyanomethyl ketones. The resulting cyanomethyl ketones were utilized for the construction of amino acid derived 3-substituted-5-amino-1*H*-pyrazoles. The protocol has also been extended to prepare five N,N′-orthogonally protected pyrazolecarboxamide tethered peptidomimetics in good yield.

Acknowledgment

We thank the University Grants Commission, New Delhi [UGC, grant No. F. No. 37-79/2009 (SR)] Govt. of India for financial assistance. M.S.K. thanks the DST, Govt. of India for the award of an INSPIRE fellowship.

References and Notes

(1) (a) Rijkers, D. T. S.; Van Esse, G. W.; Merkx, R.; Brouwer, A. J.; Jacobs, H. J. F.; Pieters, R. J.; Liskamp, R. M. J. *Chem. Commun.* **2005**, 4581. (b) Sureshbabu, V. V.; Shankar, A. N.; Hemantha, H. P.; Narendra, N.; Ushati, D.; Guru Row, T. N. *J. Org. Chem.* **2009**, *74*, 5260.

(2) (a) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York/London, **1971**. (b) Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 577. (c) Sureshbabu, V. V.; Narendra, N.; Nagendra, G. *J. Org. Chem.* **2009**, *74*, 153.

(3) (a) Sureshbabu, V. V.; Venkataramanarao, R.; Shankar, A. N.; Chennakrishnareddy, G. *Tetrahedron Lett.* **2007**, *48*, 7038. (b) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525.

(4) Tam, A.; Arnold, U.; Soellner, M. B.; Raines, R. T. *J. Am. Chem. Soc.* **2007**, *129*, 12670.

(5) (a) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (b) Huisgen, R. *1,3-Dipolar Cycloaddition-Introduction, Survey, Mechanism*, In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**, 1–176. (c) Falorni, M.; Giacomelli, G.; Spanu, E. *Tetrahedron Lett.* **1998**, *39*, 9241.

(6) (a) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3169. (b) Domling, A. *Chem. Rev.* **2006**, *106*, 17.

(7) (a) Maareseveen, J. H. V.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503. (b) Pedersen, D. S.; Abell, A. *Eur. J. Org. Chem.* **2011**, 2399.

(8) (a) Abell, A. D. *Lett. Pept. Sci.* **2002**, *8*, 267. (b) Spatola, A. F. In *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*; Vol. 7; Weinstein, B., Ed.; Dekker: New York, **1983**, 267.

(9) (a) Reeder, M. R.; Anderson, R. M. *Chem. Rev.* **2006**, *106*, 2828. (b) Birch, P. L.; El-Obeid, H. A.; Akthar, M. *Arch. Biochem. Biophys.* **1972**, *148*, 447. (c) Albek, A.; Persky, R. *Tetrahedron* **1994**, *50*, 6333.

(10) Uekun, F. M.; Perrey, D. A.; Narla, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 547.

(11) (a) Beaulieu, P. L.; Wernic, D.; Duceppe, J.-S.; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317. (b) Onishi, T.; Hirose, N.; Nakano, T.; Nakazawa, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 5883.

(12) (a) Izawa, K.; Onishi, T. *Chem. Rev.* **2006**, *106*, 2811. (b) Beaulieu, P. L.; Lavallee, A.; Abraham, A.; Anderson, P. C.; Boucher, C.; Bousquet, Y.; Duceppe, J.-S.; Gillard, J.; Gorys, V.; Grand-Maitre, C.; Grenier, L.; Guindon, Y.; Guse, I.; Plamondon, L.; Soucy, F.; Valois, S.; Wernic, D.; Yoakim, C. *J. Org. Chem.* **1997**, *62*, 3440. (c) Goodman, M.; Felix, A.; Moroder, L.; Toniolo, C. *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*; Vol. E22c; Georg Thieme Verlag: Stuttgart, **2003**, 393–395.

(13) Narendra, N.; Vishwanatha, T. M.; Sudarshan, N. S.; Sureshbabu, V. V. *Protein Pept. Lett.* **2009**, *16*, 1029.

(14) Lalithamba, H. S.; Narendra, N.; Shankar, A. N.; Sureshbabu, V. V. *ARKIVOC* **2010**, *(xi)*, 77.

(15) (a) Narendra, N.; Vishwanatha, T. M.; Sureshbabu, V. V. *Int. J. Pept. Res. Ther.* **2010**, *16*, 283. (b) Rotella, D. P. *Tetrahedron Lett.* **1995**, *36*, 5453.

(16) (a) Bazewicz, C. G.; Lipkin, J. S.; Lozinak, K. A.; Watson, M. D.; Brewer, S. H. *Tetrahedron Lett.* **2011**, *52*, 6865. (b) Rappaport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, England, **1970**.

(17) (a) Jones, G. *Org. React.* **1967**, *15*, 204. (b) Robichaud, B. A.; Liu, K. G. *Tetrahedron Lett.* **2011**, *52*, 6935.

(18) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305.

(19) Sauve, G.; Mansour, T. S.; Lachance, P.; Belleau, B. *Tetrahedron Lett.* **1988**, *29*, 2295.

(20) (a) Brillon, D.; Sauve, G. *J. Org. Chem.* **1992**, *57*, 1838. (b) Sauve, G.; Le Berre, N.; Zacharie, B. *J. Org. Chem.* **1990**, *55*, 3002.

(21) Stuk, T. L.; Haight, A. R.; Scarpetti, D.; Allen, M. S.; Menzia, J. A.; Robbins, T. A.; Parekh, S. I.; Langridge, D. C.; Tien, J. H. J.; Pariza, R. J.; Kerdesky, F. A. J. *J. Org. Chem.* **1994**, *59*, 4040.

(22) Santos, F.; Sanchez-Rosello, M.; Pablo, B.; Simon-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984.

(23) Chen, C.; Wilcoxen, K. M.; Huang, C. Q.; Xie, Y. F.; McCarthy, J. R.; Webb, T. R.; Zhu, Y. F.; Saunders, J.; Liu, X. J.; Chen, T. K.; Bozigian, H.; Grigoriadis, D. E. *J. Med. Chem.* **2004**, *47*, 4787.

(24) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.;

Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347.

(25) Fancelli, D.; Berta, D.; Bindi, S.; Cameron, A.; Capella, P.; Carpinelli, P.; Catana, C.; Forte, B.; Giordano, P.; Giorgini, M. L.; Mantegani, S.; Marsiglio, A.; Meroni, M.; Moll, J.; Pittala, V.; Roletto, F.; Severino, D.; Soncini, C.; Storici, P.; Tonani, R.; Varasi, M.; Vulpetti, A.; Vianello, P. *J. Med. Chem.* **2005**, *48*, 3080.

(26) De Luca, L.; Falorni, M.; Giacomelli, G.; Porcheddu, A. *Tetrahedron Lett.* **1999**, *40*, 8701.

(27) Bagley, M. C.; Davis, T.; Dix, M. C.; Murziani, P. G. S.; Rokicki, M. J.; Kipling, D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3745.

(28) **Preparation of Boc-Protected Bromomethyl Ketones; Typical Procedure for 2a:** To a solution of diazomethyl ketone (1.8 mmol, 0.4 g) in THF, aq 47% HBr (2–3 mL) at 0 °C was added. The reaction mixture was stirred for another 2–3 min until the starting material was completely consumed. The reaction mixture was diluted with excess H_2O and the precipitated solid was filtered. A simple recrystallization (THF–H_2O) led to the analytically pure product

(29) **Preparation of Boc-Ala-[CH_2CN] 3a; Typical Procedure:** To a solution of Boc-Ala-CH_2Br (1.8 mmol, 0.5 g) in MeOH (5 mL), KCN (3.7 mmol, 0.24 g) was added at r.t. The reaction mixture was stirred for 3 h (reaction followed by TLC analysis). After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc (2 × 10 mL) and, to dispose of any excess KCN, the reaction mixture was quenched with sat. $KMnO_4$ solution and washed with excess H_2O. The organic layer was washed with brine (10 mL) and the solution was dried over anhydrous Na_2SO_4. The solvent was filtered and evaporated under reduced pressure and the product **3a** was isolated by column chromatography
Compound 3a: Yield: 89%; brownish gum; $[\alpha]_D^{25}$ –14.2 (*c* 1.0, $CHCl_3$); R_f = 0.4 (EtOAc–hexane, 3:7); IR (neat): 1650, 1745, 2243 cm^{-1}; ^1H MR ($CDCl_3$, 400 MHz): δ = 1.31 (d, *J* = 6.0 Hz, 3 H), 1.35 (s, 9 H), 3.19 (s, 2 H), 4.23 (m, 1 H), 6.8 (br, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.6, 28.0, 28.7, 56.4, 80.1, 116.5, 155.4, 205.4; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{16}N_2O_3$: 235.1059; found: 235.1062
Compound 3o: Yield: 82%; brownish gum; $[\alpha]_D^{25}$ –15.7 (*c* 1.0, $CHCl_3$); R_f = 0.4 (EtOAc–hexane, 5:5); IR (neat): 1658, 1718, 1741, 2231 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (d, *J* = 4.8 Hz, 6 H), 1.62 (m, 2 H), 1.78 (m, 1 H), 2.64 (s, 1 H), 3.70 (s, 2 H), 3.78 (m, 2 H), 3.84 (m, 1 H), 4.64 (m, 1 H), 5.12 (m, 2 H), 5.93 (br, 1 H), 7.12 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0, 22.4, 28.4, 40.4, 47.2, 57.3, 63.4, 65.1, 116.2, 127.1, 127.3, 128.3, 140.2, 155.5, 170.8, 207.2; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}N_3O_5$: 398.1794; found: 398.1792

(30) Goodman, M.; Felix, A.; Moroder, L.; Toniolo, C. *Houben-Weyl: Synthesis of Peptides & Peptidomimetics*; Vol. E22c; Georg Thieme Verlag: Stuttgart, New York, **2003**, 663–689.

(31) **Preparation of Boc-Ala-5-amino-pyrazole 4a; Typical Procedure:** To a solution of N^{α}-protected Boc-Ala-[CH_2CN] **3a** (1.8 mmol, 0.4 g) in MeOH (5 mL), hydrazine hydrate (14 mmol, 0.7 mL) was added. The reaction mixture was heated at reflux at 40 °C for 2 h (progress monitored by TLC). After cooling, the solvent was removed under reduced pressure to obtain the crude product, which was purified by column chromatography (silica gel 100–200 mesh; $CHCl_3$–MeOH, 9:1).
Compound 4a: Yield: 85%; yellowish gum; $[\alpha]_D^{25}$ –12.1 (*c* 1.0, $CHCl_3$); R_f = 0.3 ($CHCl_3$–MeOH, 9:1); IR (neat): 1740, 2874, 3429 cm^{-1}; ^{1}HNMR ($CDCl_3$, 400 MHz): δ = 1.34 (d, *J* = 8.1 Hz, 3 H), 1.40 (s, 9 H), 3.82 (m, 1 H), 5.22 (br, 2 H), 5.80 (s, 1 H), 6.21 (br, 1 H), 9.40 (br, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.2, 29.0, 48.3, 80.1, 96.3, 141.2, 155.1, 155.8; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{18}N_4O_2$: 249.1430; found: 249.1427.
Compound 4k: Yield: 78%; yellowish gum; $[\alpha]_D^{25}$ –20.5 (*c* 1.0, $CHCl_3$); R_f = 0.4 ($CHCl_3$–MeOH, 9:1); IR (neat): 1747, 1762, 2881, 3432 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, *J* = 6.3 Hz, 6 H), 1.61–1.63 (m, 2 H), 1.70 (m, 1 H), 2.43–2.54 (s, 1 H), 4.82 (br, 2 H), 5.25 (s, 2 H), 4.50 (t, *J* = 5.6 Hz, 1 H), 5.34 (s, 2 H), 5.8 (s, 1 H), 6.50 (br, 1 H), 7.11–7.23 (m, 5 H), 10.11 (br, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.3, 21.1, 38.9, 49.6, 52.3, 65.1, 65.9, 93.2, 125.7, 127.3, 128.2, 139.9, 142.1, 154.2, 155.8, 169.3; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{27}N_5O_4$: 412.1961; found: 412.1963

(32) Chiral HPLC details: Agilent 1100 series having G1311A VWD at λ = 230 nm; flow 1.0 mL/min; Column: Phenominex made Lux; pore size 5 μm; Cellusole-1, 250 × 4.6 mm; *n*-hexane–isopropanol (85:15) in isocratic mode in 40 min

(33) Dressen, D.; Garofalo, A. W.; Hawkinson, J.; Hom, D.; Jagodzinski, J.; Marugg, J. L.; Neitzel, M. L.; Pleiss, M. A.; Szoke, B.; Tung, J. S.; Wone, D. W. G.; Wu, J.; Zhang, H. *J. Med. Chem.* **2007**, *50*, 5161.

(34) Černovská, K.; Kemter, M.; Gallmeier, H.-C.; Rzepecki, P.; Schrader, T.; König, B. *Org. Biomol. Chem.* **2004**, *2*, 1603.

(35) Sureshbabu, V. V.; Hemantha, H. P. *ARKIVOC* **2008**, *(ii)*, 243.

(36) **Preparation of Pyrazole-Linked Peptidomimetic 6a; Typical Procedure:** To a solution of Fmoc-Val-Cl (0.5 mmol, 0.2 g) and NMM (0.68 mmol, 0.07 mL) in THF at 0 °C, was added Cbz-protected-Ala-5-amino-pyrazole. The reaction mixture was stirred for 2–3 h (TLC monitoring). After completion of reaction, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL), washed with citric acid (10%, 10 mL), aqueous Na_2CO_3 (10%, 10 mL), H_2O (2 × 10 mL), and brine (2 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purification by column chromatography (silica gel 100–200 mesh; $CHCl_3$–MeOH, 9:1) to afford pyrazolecarboxamides.
Compound 6a: Yield: 78%; yellowish solid; $[\alpha]_D^{25}$ +52.7 (*c* 1.0, $CHCl_3$); R_f = 0.3 ($CHCl_3$–MeOH, 9:1); IR (neat): 1659, 1766, 2886, 3423 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (m, 6 H), 1.30 (d, *J* = 4.5 Hz, 3 H), 2.01 (m, 1 H), 4.19 (d, *J* = 3.9 Hz, 1 H), 4.20 (t, *J* = 6.6 Hz, 1 H), 4.21 (d, *J* = 7.4 Hz, 2 H), 4.82 (m, 1 H), 5.01 (s, 2 H), 5.18 (m, 2 H), 5.89 (s, 1 H), 6.09 (br, 2 H), 7.25–7.77 (m, 13 H), 11.8 (br, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1, 20.2, 28.0, 42.4, 46.2, 47.5, 52.0, 58.1, 64.9, 66.8, 91.3, 124.6, 125.3, 126.1, 126.8, 127.0, 128.4, 136.1, 139.3, 140.2, 141.6, 143.0, 155.3, 155.5, 170.1; HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{35}N_5O_5$: 604.2536; found: 604.2538.

